

### DETAILED ACTION

This Office Action is written in response to Applicants' response filed 3/25/11. Claims 1-6, 8-10, 12-17, and 19-23 are pending.

#### *Claim Rejections - 35 USC § 103*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 1- 6, 8-10, 12, 14, 15, 17, 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson-Riveros et al. (US 2004/0115308) and in further view of Yang et al. (US 6,306,638), Hayakawa et al. (Journal of Fermentation and Bioengineering Vol. 70 No. 6 p 401-408), van de Guchte et al. 2002 (Antoine van Leeuwenhoek vol. 82 pgs. 187-216), and J. Vives-Rego et al. FEMS Microbiology Reviews 24 (2000) 429-448.

Regarding Claims 1, 2, and 12: Bengtsson-Riveros discloses liquid bacteria concentrates [pg. 2, para 0020; 0025] having viable bacteria at a concentration of  $1.5 \times 10^8$  to  $5 \times 10^{11}$  cfu/ml [pg. 3, para 0031]; and further discloses that the bacteria are species selected from Lactobacillus, Bifidobacterium, Streptococcus, Lactococcus [pg. 3, 0033]; and also discloses that the bacteria can be concentrated via filtration methods known in the art [pg. 4, para 0051].

Bengtsson-Riveros does not explicitly disclose that the bacteria are adapted and more resistant to various physiochemical stresses and that the adaptation of the bacteria is determined by bacteria size, and that the adaption is a reduction in size (claim 12). Bengtsson-Riveros does not disclose that size selection is performed by flow cytometry or determination of relative permittivity or microscopy.

Yang discloses adaptation of Bifidobacterium that are to be used in food products, and that the bacteria have been adapted to have increased tolerance to gastric acid and oxygen [col. 9, lines 25-35; 41-46].

Hayakawa discloses Lactobacilli grown in culture medium, and that a cross flow filtration system (tangential microfiltration) is used to wash and feed bacteria with fresh medium and to concentrate the bacteria in order to get high density cultivation of bacteria [pg 404-405 *Culture*].

van de Guchte discloses that in response to stress conditions such as cold, heat, osmotic, or acid stress, bacteria enter a stationary phase [pg. 205, "Starvation response and stress tolerance"]. van de Guchte also discloses that lactococci have adapted to stress conditions by entering in a stationary phase which leads to a diminution in cell size [pg. 205, 2<sup>nd</sup> column, top paragraph continuation of previous column].

Vives-Rego discloses using flow cytometry to determine cell size [abstract].

At the time of the invention it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, and Vives-Rego before him or her to modify the bacteria of Bengtsson-Riveros to include adapted bacteria because this would have allowed for the selection of bacteria having the ability to maintain its viability during periods of extended storage and to allow the bacteria to survive passage through the stomach (gastric acid) in order to provide its beneficial effect by maintaining healthy microflora in the intestines [Yang, col. 1, lines 24-32, col. 9, lines 25-46; van de Guchte pg. 188; 1<sup>st</sup> column].

Further, it would have been obvious to modify the culture of bacteria in Bengtsson-Riveros to include a continuous culturing process where the bacteria are washed/fed fresh medium and concentrated using cross-flow filtration (tangential microfiltration) because it avoids plugging of the membrane found in traditional filtration systems [Hayakawa, pg 404 Abstract] and allows for

the maintenance of preferred pH ranges because of the lack of lactic acid build up from the proliferating cells, and increases the amount of cells cultivated because the process helps maintain an environment favorable for growth [Hayakawa, pg 404 Abstract].

Further, it would have been obvious to use bacteria size as a way of selecting for adapted bacteria since van de Guchte discloses that in response to stress conditions, bacteria such as lactococci, are known to decrease in size in order to survive stress conditions.

Further it would have been obvious to utilize flow cytometry to determine the cell size in order to provide accurate selection of adapted bacteria because flow cytometry has assorting capacity that allows for the transfer of specific populations or single cells to a location.

**Regarding Claims 3 and 4:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses that the bacteria have a survival rate of above 80% even after 90 days of storage at 20°C with children's breakfast cereal [pg. 7, Table 16]. The 80% figure was computed from the 90 day viable cfu count versus the starting cfu count [pg.7, Table 16]. Although Bengtsson-Riveros does not explicitly disclose the pH of the cereal being between 3 and 7, it is well known in the art that cereals have a pH between 5 and 6. Further Bengtsson-Riveros discloses in vitro testing of bacteria showing the ability to withstand gastric and bile acids [pg.2 para. 0027] which is within the pH range of the instant claims.

Further, claims 3 and 4 claim characteristics of the liquid bacterial concentrate of claim 1. Since the limitations of claim 1 have been met it would have been obvious to one of ordinary skill in the art that when the adapted liquid bacterial cultures were concentrated by tangential microfiltration as discussed above, the bacteria would have exhibited the characteristics as disclosed in claims 3 and 4.

**Regarding Claim 5:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses that the liquid bacteria concentrate can be added to beverages [pg.4, para 0049].

**Regarding Claim 6:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses that the liquid bacteria concentrate is viable up to 1 year [pg.4, para 0049].

Although Bengtsson-Riveros does not disclose the viability of the bacteria being between 4 to 6 weeks it does disclose that the bacteria are viable for up to 1 year (up to 52 weeks) thereby encompassing and surpassing the 4 to 6 week requirement of the claim, therefore, one having ordinary skill in the art at the time the invention was made would have considered the invention to have been obvious because the compositional proportions taught by Bengtsson-Riveros overlap the instantly claimed proportions and therefore are considered to establish a prima facie case of obviousness. *In re Malagari* 182 USPQ 549,553.

**Regarding Claims 8 and 9:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above. Bengtsson-Riveros does not explicitly disclose where the bacteria are adapted based upon parameters of the bacteria or the bacterial culture medium.

Yang discloses where parameters for determining adaptation are based upon pH tolerance and oxygen tolerance of the bacteria [col.7, lines 40-44].

At the time of the invention, it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, and Vives-Rego before him or her to measure the adaptation of the bacteria based on pH in order to determine whether the bacteria used in the food product would have be able to withstand an acidic environment in order for the bacteria to be useful as probiotics.

**Regarding Claim 10:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above. Bengtsson-Riveros does not disclose where the parameter of the culture medium is pH and the adaptation step is performed by reducing the pH by natural acidification.

Yang discloses bacterial adaptation as discussed above but regulates the pH by adding acids to the medium.

Hayakawa discloses bacteria that are maintained via cross-flow filtration in a particular culture medium where the pH is maintained based on the amount of glucose present in the culture medium and the amount of pH lowering lactic acid being produced [pg. 407, and Fig. 7].

At the time of the invention it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, Vives-Rego before him or her to modify the method of adaptation as disclosed in Yang to include the adaptation using natural acidification as disclosed in Hayakawa in order to maintain the desired pH within a sterile environment so that the concentrated bacteria can be directly added to food products or directly packaged for later addition to food products.

**Regarding Claim 14:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above. Bengtsson-Riveros does not explicitly disclose where the pH of the concentrate is between 3 and 6.

Yang discloses that the pH of medium for storage of bacteria concentrate is 6.2 to 6.5 [col. 9, lines 64-67; col. 10, lines 1-14] and further discloses where the pH of the culturing medium could be from 5 to 9 [col. 10, lines 46-50].

At the time of the invention, it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, and Vives-Rego before him or her to include the concentrate at the pH as disclosed in Yang in order to maintain the

bacteria in a slightly acidic environment to maintain a favorable environment for bacteria that have been adapted for a more acidic environment.

Further regarding the pH of the storage medium, although Yang does not disclose where the pH is between 3 and 6 as in the instant claim, the ranges disclosed are substantially close to that of the instant claims, one of ordinary skill would have expected compositions that are in such close proportions to those in prior art to be prima facie obvious and to have same properties. *Titanium Metals Corp.*, 227 USPQ 773 (CAFC 1985).

Further regarding the pH of the culture medium, although Yang does not disclose where the pH is between 3 and 6, one having ordinary skill in the art at the time the invention was made would have considered the invention to have been obvious because the compositional proportions taught by Yang overlap the instantly claimed proportions and therefore are considered to establish a prima facie case of obviousness. *In re Malagari* 182 USPQ 549,553.

**Regarding Claim 15:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses freezing them after packaging [pg. 2, para 0020, pg. 3, para 0041], where the instant claim recites preserving at temperature between -50°C and 4°C after packaging.

Although Bengtsson-Riveros, does not explicitly disclose preserving at temperatures between -50°C and 4°C after packaging, it is well known in the art that freezing occurs at temperatures from 0°C and below and that at such temperatures products that are subject to degradation are preserved, therefore the recitation of the freezing the packaged material satisfies the limitations of the claim.

**Regarding Claims 17, 20, 21:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses that the liquid concentrate is added to food additives and food

products, and beverages such as cereal powders, powdered milk, chocolate, cereals, and beverages [pg. 4, para 0049].

**Regarding Claim 22:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses that the bacteria can be directly added to the consumable product and stored with the consumable product [pg. 2, para 0024] and further discloses adding probiotics to the consumable product before packaging the product [pg. 3, para 0040].

**Regarding Claim 23:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses that the bacteria can be applied to the consumable product by spraying [pg. 2, para 0020]. Although Bengtsson-Riveros does not explicitly state the liquid concentrate is added by pumping, that action of spraying onto the consumable product involves a pumping action and therefore satisfies the limitation of the claim.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a spraying device because it involves pumping action and is commonly used to distribute liquid products that will be applied directly to food and since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of obvious engineering choice. *In re Leskin* 125 USPQ 416

2. **Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson-Riveros et al. (US 2004/0115308), Yang et al. (US 6,306,638), Hayakawa et al. (Journal of Fermentation and Bioengineering Vol. 70 No. 6 p 401-408), and van de Guchte et al. 2002 (Antoine van Leeuwenhoek vol. 82 pgs. 187-216) and J. Vives-Rego et al. FEMS Microbiology Reviews 24 (2000) 429-448 as applied to claim 1 above, and in further view of McDaniel (US 2004/0175407).**

**Regarding Claim 13:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above. Bengtsson-Riveros does not disclose where the lengths of the bacteria are between 0.1 to 10  $\mu\text{m}$ .

McDaniel discloses that species of *Lactobacillus* have lengths in the range of 1.0 -10  $\mu\text{m}$ , species of *Bifidobacterium* have lengths in a range of 1.5 - 8.0  $\mu\text{m}$ , species of *Streptococcus* have lengths in a range of 0.5 – 2.0  $\mu\text{m}$ , species of *Lactococcus* have lengths in the range of 0.5 -1.5  $\mu\text{m}$  [pg 21, Table 3].

At the time of the invention it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, Vives-Rego, and McDaniel before him or her to include bacteria having lengths of between 0.1 to 10  $\mu\text{m}$  since these are physical characteristics exhibited by the preferred bacteria of the invention which are disclosed in Bengtsson-Riveros, Yang, Hayakawa, and van Guchte (*Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Lactococcus* [pg. 3, 0033]) .

3. **Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson-Riveros et al. (US 2004/0115308) and Yang et al. (US 6,306,638) and Hayakawa et al. (Journal of Fermentation and Bioengineering Vol. 70 No. 6 p 401-408), and van de Guchte et al. 2002 (Antoine van Leeuwenhoek vol. 82 pgs. 187-216), and J. Vives-Rego et al. FEMS Microbiology Reviews 24 (2000) 429-448 as applied to claims 1 and 15 above and in further view of Rinfret et al. (US 3,228,838).**

**Regarding Claim 16:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses thawing them after freezing [pg. 2, para 0020, pg. 3, para 0041]. Bengtsson-Riveros does not explicitly disclose reheating to a temperature between 25°C and 45°C.



Rinfret discloses preserving biological substances such as blood, bacteria, yeast, beverages from degradation by freezing and then thawing at 37 °C [col. 1, lines 16-20; col. 7, lines 13-37].

At the time of the invention, it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, Vives-Rego, and Rinfret before him or her to thaw the bacteria at 37 °C because doing so would bring the bacteria to a temperature that is favorable to maintaining their viability [Rinfret, col. 3, lines 16-19].

4. **Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson-Riveros et al. (US 2004/0115308), Yang et al. (US 6,306,638), and Hayakawa et al. (Journal of Fermentation and Bioengineering Vol. 70 No. 6 p 401-408), and van de Guchte et al. 2002 (Antoine van Leeuwenhoek vol. 82 pgs. 187-216), and J. Vives-Rego et al. FEMS Microbiology Reviews 24 (2000) 429-448 as applied to claim 1 above and in further view of Bensel (US 2,364,049).**

**Regarding Claim 19:** Bengtsson-Riveros discloses liquid bacteria concentrates as discussed above and further discloses where the liquid concentrate is packaged in a hermetically sealed bag in order to preserve the product and to maintain the shelf life of the product [pg. 3, para 0040], therefore it can be inferred that given this description, the product is sterile because of the maintenance of shelf life and water activity and that the bag is flexible since flexibility is a physical characteristic of bags however these limitations are not explicitly disclosed.

Bensel discloses packaging perishable items by sterilizing them and loading into flexible heat scalable bags [pg. 2, lines 53-58].

At the time of the invention it would have been obvious to one of ordinary skill in the art having the teachings of Bengtsson-Riveros, Yang, Hayakawa, van de Guchte, Vives-Rego and Bensel before him or her to package the liquid concentrate in flexible hermetically sealed, sterile packaging

because it would prevent the degradation of the liquid concentrate (maintain the shelf life) and prevent contamination with undesirable pathogenic bacteria or bacteria that have not been adapted for use as probiotics.

### ***Double Patenting***

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 2, 8-10, 12, 15, 16, 19 and 22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-9, 18, 19, 20, and 28 of copending Application No. 10/590,658. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed toward adapted liquid bacterial concentrates that are treated by tangential microfiltration; where the bacteria are *Lactobacilli*, *Bifidobacterium*, *Streptococcus*, or *Lactococcus*; where the parameters are measured by the medium or bacteria; where the bacteria is added at the end of a production line and packaged in flexible hermetically sealed bags and can be reheated after packaging.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

3. Applicant's arguments filed 3/25/11, with respect to the rejections of the claims have been fully considered and are persuasive in light of the amendment made to claim 1. Therefore, the rejection has been withdrawn. However, upon further consideration, new grounds of rejection are made as discussed in the above office action.

4. Further the Examiner disagrees with Applicants' assertion that the arguments made by the Examiner relies upon an unsupported assumption. The Applicants assert that the Examiner has extended the starvation response discussed in the van de Guchte reference to all physiochemical stress responses and that is incorrect to assume that a modification in cell size occurs in other stressors.

5. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a specific type of physiochemical stress) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants have not defined physiochemical as something other than starvation. Claim 1 recites "various physiochemical stresses". Examiner does agree nutrient starvation is not the only type of stress that cells undergo. However, starvation by inadequate nutrients is a physiochemical stressor.

***Conclusion***

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FELICIA C. KING whose telephone number is (571)270-3733. The examiner can normally be reached on Mon- Thu 7:30 a.m.- 5:00 p.m.; Fri 7:30 a.m. - 4:00 p.m. alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Humera Sheikh can be reached on 571-272-0604. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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